Temporal Profile of Neurochemical Recovery Following Injury by Transient Cerebral Ischemia

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The effects of transient cerebral ischemia by the four-vessel occlusion model on balance beam performance and regional activity of glutamic acid decarboxylase (GAD) and choline acetyltransferase (ChAT) and muscarinic binding (MusBnd) were evaluated over a six-month postischemia period in 6- and 24-month-old rats. Cerebral ischemia resulted in an early reduction in balance beam performance in young and old rats that partially recovered. GAD in young and old animals and ChAT in old animals and MusBnd in young and old animals were also significantly altered by ischemia. There was partial recovery of each neurochemical marker noted. In some cases the recovery was partially accounted for by the absence of any age-associated changes in the ischemic group. The results of the present study suggest an age-dependent vulnerability to ischemic injury occurs and that the aged brain’s γ-aminobutyric and cholinergic systems are capable of measurable recovery.

We have previously shown the short-term effects of age and transient cerebral ischemia on the activity of two neurotransmitter synthetic enzymes in four regions of the brain (Nyberg and Waller, 1989). The enzymes, glutamic acid decarboxylase (EC 4.1.1.15; GAD) and choline acetyltransferase (EC 2.3.1.6; ChAT), are the synthetic enzymes for the neurotransmitters γ-aminobutyric acid (GABA) and acetylcholine (ACH), respectively, and are predominantly located in the nerve terminal. In that study, the activity of GAD was reduced in the cortex, hippocampus, striatum, and cerebellum in young (6 and 12 months old) and old (24 months old) rats after thirty minutes of cerebral ischemia and five days recovery. The reduction in GAD activity following the ischemic challenge was greater in the older group of animals compared with the younger animals. In the same animals, regional ChAT activity was unaffected by the ischemic challenge in young animals, but was markedly reduced in the older animals. These findings suggested an age-dependent vulnerability for neurons containing either GAD or ChAT.

This report further describes the effects of transient cerebral ischemia on the activity of GAD and ChAT, but also includes effects on muscarinic binding. The purpose of this study was threefold. The first purpose was to extend the earlier findings of age-dependent vulnerability to ischemia-reduced changes observed for ChAT by including another marker of the central cholinergic system, muscarinic binding. We have shown earlier that in Fischer 344 rats a statistically significant positive correlation between ChAT activity and muscarinic binding is observed. The second purpose was to characterize the temporal profile of the changes and to determine approximately when the damage is maximal. The third purpose was to assess whether the aging brain is less able to recover from the effects of ischemia.

MATERIALS AND METHODS

We used male Fischer 344 rats aged 6 or 24 months at the start of the experiment, obtained from the contract rodent colonies of the National Institute on Aging (Bethesda, MD). Rats were accommodated in groups of five to seven per cage in the animal care facility. The facility was maintained at 23 ± 5 °C with a 12-hr light (0600 to 1800, CST):12-hr dark photoperiod. Animals had been acclimated to the vivarium for at least 45 days before the start of the experiment. Purina rodent chow and demineralized tap water were available ad libitum.

By using the method of Pulsinelli and Brierley (1979), transient cerebral ischemia was produced in rats by occluding the four major arteries supplying the brain. In this model of transient cerebral ischemia, both vertebral arteries were cauterized, and reversible occluders (OC-2, In Vivo Metric Systems, Heraldsburg, CA) were placed around the common carotid arteries without disturbing carotic blood flow. All surgical manipulations were performed under pentobarbital (55 mg/kg, intraperitoneal) anesthesia using sterile techniques. Forty-eight hours after surgery, one-half of the surgically prepared rats were restrained by gloved hand, and carotid artery blood flow to the brain was interrupted for exactly 30 minutes by closure of the occluder. This was the ischemia group. The remaining surgically prepared animals were handled similarly but without interruption of carotid blood flow to the brain. This was the control group. A third surgically naive group was included in the study to assess the effects of surgery on the balance beam performance and
neurochemical markers. This was the naive group. It should be noted that the reversible vascular occluders were removed for all animals between 10 and 14 days after surgical implantation. This was necessitated by slow tissue encapsulation of vascular occluders that would occlude the artery if allowed to progress.

Groups of five or six rats at each time period were evaluated for balance and coordination using a simple balance beam procedure immediately before the disruption of carotid blood flow and 0.5, 1, 4, 12, 16, 20, or 24 weeks after the ischemia procedure outlined above. In the balance beam test, the ability of a rat to maintain balance on a 2-cm diameter scored wooden dowel suspended 24 cm above a bed of wood shavings was assessed. The unit for this measure was seconds remaining on the beam with a maximal duration of 60 seconds (a perfect score). The mean time on the beam across four trials (with 60-second intertrial intervals) is the measure of performance in this task in each rat.

Rats were killed immediately after the balance beam performance assessment, brains were rapidly removed, and the frontal/parietal cortex, hippocampus, striatum, and cerebellum were dissected out. Each region was homogenized in 20 volumes (wt/vol, 1 mg/20 μl) of .32 M sucrose. Choline acetyltransferase (ChAT) and glutamic acid decarboxylase (GAD) activities were measured radiometrically by the methods of Bull and Oderfeld-Nowak (1971) and Wilson et al. (1972), respectively, as modified by Nyberg and Waller (1989). The concentrations of all substrates and cofactors used in these assays were in excess, suggesting that the activities presented would approximate maximum enzymatic reaction velocity (V_{max}). Muscarinic binding was measured radiometrically using [3H]-quinuclidinyl benzilate ([3H]QNB) in a modification of the method of Ikeda et al. (1980). Standard incubations contained 250 μg protein and 1.75 nM [3H]QNB with a final incubation volume of 1.0 ml. Incubations were for 90 minutes at room temperature and were stopped by filtration. Nonspecific binding, assayed in the presence of 100 μM oxotremorine, was subtracted from total binding. Given these conditions, [3H]QNB binding reported here would approximate maximum binding (B_{max}). ChAT and GAD activity and total specific [3H]QNB binding was reported in terms of supernatant protein, which was assayed by the BioRad method.

The effects of age and treatment were assessed by analysis of variance. Comparisons between treatments were always made between similarly aged animals. It should be noted that unless specified otherwise, the term age-matched refers to animals matched by treatment age (young or old) and by test period (0, .5, 1, 4, 12, 16, 20, and 24 weeks following restoration of cerebral blood flow). When the value of F showed significance, individual means were compared by the Tukey’s HSD test. All statistical comparisons were made using the SYSTAT (Systat Inc., Evanston, IL) computer program. The criterion for significance was p ≤ .05.

RESULTS

There were no statistically significant differences noted between the (surgery) naive and control groups for any of the measures in the study, and statistical differences between the naive and ischemic group paralleled the statistical differences observed between the control and ischemic groups. The data from naive animals are not presented, as it is redundant to the control group.

Ischemia resulted in an increased mortality rate in both young and old animals. The mortality rate observed was 45% in the young ischemic group and 85% in the old ischemic group during the 24 weeks of the present experiment. This was higher than the 15 and 60% mortality rates observed in the young and old control and surgery naive groups for the 24-week test period.

Cerebellar GAD and ChAT activity and muscarinic binding in the four experimental groups are shown in the upper three graphs of Figure 1, respectively. Young control values for all three markers and old control GAD activity were stable between recovery groups in this study. ChAT activity and muscarinic binding in old control animals significantly declined by 18 and 12% respectively, over the course of the study. GAD activity following restoration of cerebral blood flow was approximately 49% lower in young and old ischemic animals compared to age-matched control animals and remained at this level for the duration of the study. The
difference in GAD activity between age-matched control and ischemic animals was statistically significant at all ischemia recovery test periods in both young and old animals. Young control and ischemia values for ChAT activity and muscarinic binding were not significantly different at any test period. Ischemia was associated with a significant reduction in ChAT activity in old animals compared with age-matched control ChAT activity. More specifically, ChAT activity was reduced to 86% of age-matched control activity at the 0.5-week recovery period and to 81% of age-matched control at the 1-week recovery period. Although the absolute level of activity remained at approximately 37 nmol acetylcholine produced per hour per mg protein for the next four recovery periods (4–20 weeks), the difference between ischemia and control decreased due to the age-related decline of ChAT activity in control animals. The difference by the 20 weeks recovery period was only 12%, although this difference was still statistically significant. At 24 weeks of recovery, old ischemia ChAT activity was 101% of age-matched control and was not statistically different. Muscarinic binding in the old ischemic group was higher than age-matched control binding at all recovery periods tested in the present study, although the difference was statistically significant only at the 12, 16, 20, and 24 weeks recovery periods. The bottom graph of Figure 1 shows balance beam performance of the four treatment groups in this study. Both young and old control balance beam performance was stable over the 24 weeks covered by this study. In the young ischemic group, performance on the balance beam at the 0.5- and 1-week recovery period was approximately 11% of age-matched control performance. In the 4-week recovery period groups, performance in the young ischemic animals rebounded to 58% of age-matched control performance. Performance in the young ischemic animals following 12 weeks of recovery was lower than that observed in age-matched control animals, but not statistically different. In the old ischemic animals, balance beam performance was approximately 6% of age-matched control animal performance after 0.5 and 1 week of recovery. Old ischemic animal performance rebounded to 37% of age-matched control performance by the fourth recovery week and continued rebounding in subsequent test periods, reaching 72% of age-matched control performance in the 24 weeks recovery ischemic group. All performance levels in the old ischemic animals following the restoration of cerebral blood flow were significantly lower than age-matched control balance beam performance. The balance beam performance of the four treatment groups is presented with the temporal parallels (or lack of) between neurochemical and performance changes. The balance beam performance graph is also included with the remaining three figures for the same reason.

The temporal profiles of cortical GAD and ChAT activity and muscarinic binding in the four treatment groups are shown in Figure 2. Young control values for all three markers were stable over the course of the study. Old control values for all GAD and ChAT activity and muscarinic binding were significantly lower by 15, 25, and 13%, respectively, comparing the measures at the start and at the end of the study. Comparing age-matched control group values to ischemic group values, ischemia significantly reduced GAD activity in both the young and old animals. GAD activity was reduced by as much as 26% in the young ischemic animals and as much as 68% in the old ischemic animals. GAD activity between age-matched control and ischemic animals at all recovery periods following the restoration of cerebral blood flow was statistically different for both young and old age groups. ChAT activity and muscarinic binding in young control and ischemic animals were not statistically significant for any of the recovery periods evaluated in this study. In old animals, ChAT activity in the ischemic group was 50% lower by the end of the first week of recovery from ischemia. The activity of ChAT in old ischemic animals remained significantly lower than age-matched
control animal activity at the 4, 8, 12, 16, and 20-week recovery periods. However, the difference between the two treatment groups diminished until the control and ischemic values were identical at the 24-week recovery period. Muscarinic binding also was significantly lower in old ischemic animals following 0.5, 1, and 4 weeks of recovery from ischemia. The binding in old ischemic animals remained lower than age-matched control animals 12, 16, and 20 weeks after the ischemia, but the difference was not significant. It should be noted that binding in the old ischemic animals was stable between 0.5 week and 20 weeks of recovery, whereas binding in the control group declined. However, between the 20th and 24th week of recovery from ischemia, muscarinic binding in the old ischemic group increased 7%, whereas binding in the old control group decreased by 14%. Combined, these changes resulted in muscarinic binding in the old ischemic group that was significantly higher by 22%.

The long-term effects of 30 minutes of ischemia on GAD and ChAT activity and muscarinic binding in the hippocampus of young and old rats are shown in Figure 3. The activity of GAD was 18% lower, ChAT activity was 25% lower, and muscarinic binding was 15% lower in the control group tested 24 weeks after the start of the study compared to the group tested at the start of the study. The difference was statistically significant starting in the 16-week group for GAD activity and muscarinic binding and in the 12-week group for ChAT activity. GAD activity in both young and old ischemic rats was significantly lower compared to age-matched control rats' activity at all posts ischemia testing periods. It should be noted that the difference between the old control and old ischemic animals diminished as the experiment progressed, largely because of the age-related decline in control GAD activity, although significance was maintained throughout the study. ChAT activity in young ischemic animals was not significantly different from age-matched control animals at any of the recovery sampling periods. In contrast, ChAT activity in old ischemic animals was significantly lower following 1 week of recovery compared to age-matched control rats. At the 1-week recovery period, ChAT activity in control old animals was 95 ± 9 nmol acetylcholine produced per hour per mg protein, whereas ChAT activity in ischemic old animals was only 59.5 ± 5 nmol acetylcholine produced per hour per mg protein. This level of activity reduction was observed following 4 and 12 weeks of recovery. ChAT activity in the old ischemic group increased starting 16 weeks after the ischemia, and the difference between old control and ischemic animals was not statistically significant 20 and 24 weeks following cessation of ischemia. Muscarinic binding in both young and old ischemic animals was significantly lower than age-matched control binding at the 0.5, 1, 4, and 12-week recovery periods. However, the differences between the two groups at the 16, 20, and 24-week recovery periods were not significantly different between the two age-matched treatment groups.

Figure 4 shows the effects of ischemia on striatal GAD and ChAT activity and muscarinic binding in young and old rats. GAD activity in both young and old control animals and ChAT activity and muscarinic binding in young control animals were stable across the 24 weeks of this study. ChAT activity and muscarinic binding in old control animals declined by approximately 25 and 19%, respectively, over the course of the study. Ischemia resulted in significant reduction in striatal GAD activity in both young and old rats at all posts ischemia test periods. GAD activity reached a nadir of 58% of age-matched control activity in young rats and 29% of age-matched control activity in old rats, both at 4 weeks of reperfusion. GAD activity remained constant after that in both young and old ischemic groups. ChAT activity in the young ischemic group was not statistically different from the corresponding activity in the young control group. Striatal ChAT activity in the old ischemic group was significantly higher by 22%.
RECOVERY AFTER TRANSIENT CEREBRAL ISCHEMIA

Figure 4. Effects of transient cerebral ischemia on striatal glutamic acid decarboxylase (GAD) (top graph) and choline acetyltransferase (ChAT) (second graph) activity and muscarinic binding (third graph) and balance beam performance (bottom graph) in 6-month-old (○, ●) and 24-month-old (▽, △) Fischer 344 rats. Control animals are symbolized by the open symbols and ischemic animals by the solid symbols. Each point represents the mean of 5–6 animals with a SEM of less than 11% (not shown). The units for GAD activity are nmol 7-aminobutyric acid produced per hour X mg protein-1. The units for ChAT activity are nmol acetylcholine produced per hour x mg protein-1. The units for muscarinic binding are fmol [3H]quinuclidinyl benzilate bound per mg protein. *Corresponding ischemic value is significantly different from the age-matched control value, p < .05.

lower following ischemia, except the activity measured 24 weeks after ischemia, where the difference was not statistically significant. Muscarinic binding in old control and old ischemic rats was not statistically different for any recovery period of the present study. In young animals, binding was lower in the ischemic group at all recovery periods, although the difference was statistically significant only in the 4, 12, 16, 20, and 24 weeks recovery groups.

DISCUSSION

In the central nervous system, the neuron is the most sensitive cell type with respect to ischemic injury (Jacob, 1963; Pulsinelli et al., 1982). Among neurons there is a difference of vulnerability to ischemic damage. Neurons in the cortex (layers 3, 5, and 6), hippocampus (h1, h3–h5, and paramedian zones), striatum (small and medium sized), and cerebellum are among the most sensitive (Pulsinelli et al., 1982). The vulnerability of neurons in each of these locations can also be classified on the basis of neurochemical markers. In 1989, we showed an age-dependent vulnerability of ChAT and an age-independent vulnerability of GAD to transient cerebral ischemia (Nyberg and Waller, 1989). The findings of the current study confirm our earlier findings. We again observed reduction in GAD activity following ischemia in cerebellum, cortex, hippocampus, and striatum in both 6- and 24-month-old Fischer 344 rats. Also in the present study, we again observed little change associated with ischemia in ChAT activity in young rats but significant reductions in ChAT activity in all four brain regions tested in old rats. We extend the observations of the earlier study by reporting complex changes in muscarinic binding following ischemia. Muscarinic binding following ischemia was transiently reduced in the cortex of old rats, elevated in the cerebellum of old rats, reduced in the striatum of young rats, and transiently reduced in the hippocampus of both young and old rats. The changes in muscarinic binding did not parallel changes in ChAT activity as would have been predicted from our earlier observations that ChAT activity correlated positively with muscarinic binding in these four brain regions of young and old Fischer 344 rats (Waller and London, 1989). However, our previous study used experimentally naive animals and it is possible that the lack of correlation between ChAT activity and muscarinic binding observed in the present study is the result of ischemic pathology.

There have been previous reports of changes in GABAergic markers following transient cerebral ischemia, although most of these used young animals and gerbil-based models of ischemia (Francis and Pulsinelli, 1982, 1983; Schlander et al., 1988; Johansen et al., 1989). The previous studies of presynaptic GABA neurochemical markers generally agree with the findings of the present study (Francis and Pulsinelli, 1982; Schlander et al., 1988; Johansen et al., 1989). In general, presynaptic markers of the GABAergic system are altered by ischemia consistent with neuronal vulnerability to ischemic damage. Specifically, the activity or presence of GAD measured posts ischemia is less than what has been observed in ischemia-naive animals (Francis and Pulsinelli, 1982; Schlander et al., 1988; Johansen et al., 1989; Nyberg and Waller, 1989). It should be noted that the present study did not attempt to delineate cell types or areas within the four brain regions of the rat. Studies by Schlander et al. (1988) and Johansen et al. (1989) suggest that, at least within the tissue we extracted as the hippocampus, the possibility exists for variation in the vulnerability of GAD based on location and cell type.

The effects of cerebral ischemia on pre- and postsynaptic markers of central cholinergic status also have been characterized in previous studies, often in young animals and in gerbil models of ischemia (Francis and Pulsinelli, 1982; Onodera et al., 1987; Nyberg and Waller, 1989; Araki et al., 1991; Haba et al., 1991; Hara et al., 1991; Bertrand et al., 1992). Previous reports of the effects of ischemia on ChAT activity have shown an insensitivity of the marker to ische-
The primary focus of this study was the long-term changes following an ischemic experience up to a total of six months posts ischemia. Previous studies of the long-term changes in GAD or ChAT activity or muscarinic binding associated with ischemia have limited the posts ischemia study period to one month or less (Onodera et al., 1987; Johansen et al., 1989; Haba et al., 1991; Ogawa et al., 1991). In addition, most of these studies used gerbils, making comparison to the Fischer 344 rats in the present study difficult. However, in general these earlier studies reported delayed and persistent or short-lived deficits in affected neurochemical markers following ischemia. A simple test of psychomotor performance was included as a method for assessing the effects of ischemic injury. The balance beam used in the present study was only 2.0 cm in diameter and represented a more difficult balance and coordination task than the 2.5- or 3.0-cm diameter beam we normally use with rats. The use of the smaller balance beam experimentally exaggerated the balance and coordination deficits resulting from the ischemia and enhanced the likelihood the motor defects would be measured following ischemia, especially in the older animals. Both young and old rats demonstrated a marked fall in balance beam performance (time on the beam) 0.5 weeks after the ischemia. Thereafter in the ischemic rat groups, performance on the balance beam task increased. The balance beam performance of young ischemic rats recovered to normal (young control) levels by the 12th week of reperfusion, whereas the performance of old ischemic rats recovered to approximately 72% of age-matched control performance by the end of the present study. The balance beam performance in aged rats appeared to be approaching the control level of performance at the end of the present study. The gradual approach to control levels of performance by the aged ischemic group was the result of increased time on the balance beam by the ischemic group and decreased time on the balance beam by the control group. It is possible that the activity of the aged ischemic animals would have converged had additional posts ischemia time been permitted. This is not the first study to report recovery of performance using a task disrupted by ischemia. For example, Genovese et al. (1992) reported recovery of behavioral performance during a 45-day posts ischemia test period on two tests of schedule-controlled behavior that were disrupted by ischemia, albeit the recovery of one of two tasks used was only partial. Tominaga and Ohnishi (1989) also measured balance beam performance following focal ischemia using a larger (3.2 cm) diameter beam and reported early posts ischemia deficits in motor performance that disappeared within seven days of the restoration of cerebral blood flow. The difference in the findings of the present study where the deficits in balance beam performance persisted and the transient disruption of performance reported by Tominaga and Ohnishi (1989) may be related to the present study’s use of a smaller diameter balance beam (2 cm vs 3.2 cm), a 30-minute period of global cerebral ischemia (vs one hour of focal ischemia), or a different strain of rat (Fischer 344 vs Sprague-Dawley).

Recovery of neurochemical markers during the 24 weeks of posts ischemia cerebral reperfusion was also observed in the present study. The activity of GAD was affected by ischemia in all four brain regions tested and in both age...
groups. However, there was little evidence for recovery of GAD activity toward preischemic values noted in any of the treatment groups, with the possible exception of the small increase in GAD activity observed in the cortex of young ischemic animals (Figure 2). This was not the case with ChAT activity or muscarinic binding in the aged ischemic group in the cortex. The levels of these two neurochemical markers of the central cholinergic system appeared quite dynamic for the entire 24 weeks of posts ischemic cerebral reperfusion. For example, in the hippocampus of rats in the aged ischemic group (Figure 3), ChAT activity and muscarinic binding were initially reduced following ischemia, but recovered to levels not statistically different from control within 16 weeks. The recovery process of these measures in the present study was not simply a consequence of ChAT activity or muscarinic binding increasing with time, but rather included the added factor of age-associated changes that occurred in the control groups over a 6-month period. More specifically, the recovery of some of the neurochemical markers was assisted to some extent by the age-associated decline in ChAT activity and muscarinic binding in the control animals, but not the ischemia animals. This is best illustrated by the recovery of ChAT activity in the cerebellum of old rats following ischemia (Figure 1). ChAT activity between 1 week (nadir of deficit) and 24 weeks (end of study) increased in the ischemic group by 9%, whereas ChAT activity during the same period declined by 14% in the control group. It is interesting that no ischemic group was observed to experience an age-associated change over the course of the study. The absence of any age-associated changes in the ischemic group could be an expression of ongoing compensatory changes or the result of selective ischemic destruction of those neurons lost in the aging process.

The observation of the present study of balance beam performance and neurochemical marker recovery following cerebral ischemia in both young and old animals is quite interesting. However, the present study focused on events that were largely age-related, specifically the cholinergic vulnerability to ischemic injury, and it would be reckless to make blanket comparisons regarding the ability of the young and aged brain to recover from ischemic injury. The most favorable situation for such a comparison in the present study is the recovery of balance beam performance in the two groups of ischemic animals. The temporal profile of recovery between the two age groups is remarkably similar, with the fastest period of recovery occurring between 1 and 4 weeks posts ischemia in both age groups. Recovery of balance beam performance in old animals was less complete than that observed for the young animals, although it is possible that given additional time the old animals would also regain normal levels of performance. Clearly, the present study has demonstrated the ability of the aged brain to partially recover from ischemic injury if provided adequate time. These findings are consistent with the hypothesis that aging selectively reduces and/or slows the ability of the brain to adapt or recover from insults such as ischemia.

Although both balance beam performance and neurochemical markers in ischemic animals recovered toward preischemic values over the 24 weeks of the study, there was no apparent relationship between the two changes or between ChAT activity and muscarinic binding. The absence of a relationship between ChAT activity and muscarinic binding was particularly disappointing, given our previous report of a strong positive correlation between these two cholinergic markers in young and old Fischer 344 rats (Waller and London, 1989). The positive correlation between the two cholinergic markers was evident in the young and old control animals, although the small number of animals used in the present study limited the level of statistical significance to \( p \leq 0.10 \) (data not shown). The absence of the relationship between the two cholinergic markers following ischemia would suggest relationships between neurochemical markers may be dynamic and can be altered by pathological situations, such as ischemia.

The observations of the present study support three conclusions. First, an age-dependent vulnerability to ischemic injury occurs, although the reason why is not evident from the present study. As was proposed by us in an earlier study, it is possible that the neurons sensitive to ischemia as a function of age have been compromised by some other age-related process. Second, the aged brain’s GABAergic and cholinergic systems are capable of measurable recovery following injury by ischemia, as are the neuronal processes regulating balance beam performance. Third, the positive correlation previously reported between regional ChAT activity and muscarinic binding was not maintained by the ischemia-injured brain in the present investigation, suggesting a dissociation effect by the ischemia.

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Nathan Shock New Investigator Award, 1995

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Dr. Andersen was honored for her innovative research in creating transgenic mice that overproduce the enzyme monoamine oxidase-B (MAO-B) in neurons, which are models for oxidative damage as observed in Parkinson’s disease. These transgenic mice will also be useful in studying whether preventative antioxidant vitamin treatment is warranted.